

CASE REPORT

Rare case of live born with confirmed mosaic trisomy 17 and review of the literature

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Funding Information

No sources of funding were declared for this study.

Received: 11 May 2015; Revised: 17 August 2015; Accepted: 20 August 2015

Clinical Case Reports 2016; 4(4): 420–424

doi: 10.1002/ccr3.397

Key Clinical Message

This article describes both previously reported as well as new phenotypic features in a trisomy 17 mosaic patient. The gold standard for postnatal diagnosis remains fibroblast analysis, though the level of mosaicism does not correlate with prognosis. A normal ultrasound in the setting of positive amniocentesis appears a reassuring indicator.

Keywords

Aneuploidy, mosaic, Trisomy 17.

Introduction

Trisomy 17 mosaic is a rare autosomal trisomy with only 28 cases previously detected by amniocentesis [1]. Full Trisomy 17 has never been observed in live borns, and is found in only 0.1% of spontaneous abortions [2]. Of those detected by amniocentesis prenatally, most mosaic cases (19/28) have demonstrated no anomalies at birth and remained thereafter without corresponding evidence of aneuploidy in fibroblasts or blood specimens. Though this still accounts for a majority, it is possible that abnormal fetuses or live born infants generate more reporting than isolated positive amniocentesis findings. This deflates the calculated likelihood of a normal birth after mosaicism is found on amniocentesis based on cases from the known literature. To date 12 reported cases have been confirmed in fibroblasts after birth [1, 3–9]. Postnatal diagnosis has proven itself dependent on fibroblast analysis. Lymphocyte karyotypes of most reported cases of Trisomy 17 have been normal [3, 10]. This is possibly due to strong selection against trisomic cells, a postzygotic event occurring after precursors of blood lymphocytes differentiate, or trisomy 17 being lost during the culturing process [3, 8]. Most of trisomy 17 reported seems to be attributed to placental mosaicism.

Amniotic cells are known to have fetal fibroblastic origin [5].

Of the 12 cases confirmed postnatally, eight had prenatal ultrasounds performed. One case reported normal results, whereas the remaining seven showed ultrasound findings of IUGR, nuchal thickening, cerebellar hypoplasia, cardiac abnormalities, asymmetric anomalies, foot position abnormalities, pleural effusions, and single umbilical artery [1, 8, 11]. Notable postnatal clinical findings for the 12 cases include cerebellar hypoplasia, scoliosis, ventricular septal defect (VSD), growth retardation, leg length differentiation, body asymmetry, severe malformations, and intellectual disability. Earliest postnatal mortality was 9 days, whereas longest living reported patient was 9 years [3, 8].

The most recent reported contribution in 2013 offered a case of prenatal diagnosis of trisomy 17 mosaicism with early termination at 23 5/7 weeks gestation. Genetic analysis suggested origination from postzygotic mitotic error of maternal chromosome 17. Parental origin was determined by genome-wide SNP microarray analysis [1]. Many previous cases demonstrated postzygotic nondisjunction [3, 6–8].

Phenotype heterogeneity has been hypothesized as secondary to varying levels of mosaicism among patients,

different tissue distributions, and likely a small sampling bias. Physical finding severity has thus expectedly not been found to correlate with levels of mosaicism, and thus nor has degree of clinical outcome [8].

We present another case with prenatal and postnatal findings consistent with trisomy 17 mosaicism. Many features demonstrated by our patient are consistent with past cases, whereas many features have not been reported previously to our knowledge.

Clinical report

The parents of our patient were a 29-year-old G2 now P2 Puerto-Rican and Norwegian mother and a 30-year-old Caucasian father. They denied consanguinity, with an otherwise noncontributory family history without known birth defects, severe cognitive impairment, genetic conditions, recurrent miscarriages, or sudden unexplained deaths. They were originally referred to us for genetic counseling at 26 weeks gestation as parents were not interested in abortive measures, and initially were not interested in invasive testing after multiple fetal malformations were found on prenatal ultrasound and subsequent amniocentesis demonstrated 37% trisomy 17 mosaicism on chromosome microarray. Fetal ultrasound at 13 weeks identified cystic hygroma, and at 18 weeks it showed short long bones and fluid around the lungs. Imaging at 20 weeks reaffirmed these findings, with additional cerebellar cyst observed. Fetal echocardiogram showed 3.5 mm moderate-sized perimembranous VSD.

The infant was delivered at 35 ²/₇ weeks secondary to maternal cholestasis with hemolysis, elevated liver enzymes, low platelets (HELLP syndrome). Amniotic fluid was meconium stained. The infant demonstrated initial respiratory distress prompting supplemental oxygen support with eventual endotracheal intubation and surfactant administration. Echocardiogram showed persistent pulmonary hypertension of the newborn (PPHN) and muscular VSD with bidirectional flow. The infant was placed on inhaled nitric oxide (iNO) for 3 days prior to extubation to humidified high-flow nasal canula (HHFNC). Total parenteral nutrition (TPN) was initiated during his first week of life. Cultures and empiric antibiotics were initiated as well, however, no infectious process was identified.

He was born with a weight of 2.28 kg (15th percentile), length of 45 cm (25th percentile), and head circumference of 32.5 cm (50th percentile). On his third day of life, our patient exhibited very large anterior fontanelle with wide metopic suture, broad forehead, mild dorsal hypertrichosis, horizontally short palpebral fissures, and with ocular hypertelorism. His ears were normally formed without pits or tags. He had flat nasal bridge, notably

short, bulbous nose with anteverted nares, retrognathia, redundant neck skin folds, wide spaced nipples, appropriate range of motion of all joints, normal palmar creases, hypoplastic nails on upper and lower extremities, mild right foot eversion, and postaxial polydactyly on the right foot (Fig. 1).

SNP DNA microarray from blood was negative for aneuploidy. Fibroblast analysis was obtained from foreskin following circumcision and resulted 75% positive for trisomy 17 mosaicism with karyotype of 47, XY, +17 {15}/46, XY {5}.

Our patient's neonatal intensive care unit (NICU) course lasted 7 weeks prior to discharge home. During this time, several abnormalities were identified. Mild right and moderate left hydronephrosis were found on renal ultrasound. No reflux was found on voiding cystourethrogram (VCUG), and renal nuclear medicine scan with furosemide suggested appropriate renal cortical function for age. A large right inguinal hernia was found and repaired at 6 weeks of life. After his initial course of TPN and enteral tube feeds, he partially tolerated oral feeds as he displayed delays secondary to oromotor weakness and poor coordination. G-tube was therefore placed at 6 weeks of life for nutrition optimization. Due to persistent emesis, additional Nissen fundoplication surgery was performed months later. He demonstrated marked hypotonia during initial months of life. Abdominal ultrasound showed normal sonographic appearance of liver and gallbladder. Head ultrasound showed no obvious abnormality, however, magnetic resonance image (MRI) of the brain showed multiple small peri-falx hemorrhages, predominant vermian hypoplasia with mild cerebellar hemisphere, and pons hypoplasia. Ophthalmology examination revealed left optic nerve atrophy, though without significant retinopathy of prematurity (ROP). Primary series of plain films showed butterfly vertebrae at T6–T8 and asymmetric vertebral bodies. Initial concerns of foot eversion were not corroborated by orthopedic evaluation at 2 month of life as they described patient without significant tibial or cavovarus foot deformity.

After inpatient stay, he required supplemental oxygen of ¼-1LPM to maintain oxygen saturations above 95%. Due to inability to tolerate cardiac catheterization procedure and recovery at 3 months of life, tracheostomy was performed for chronic respiratory failure. Repeat MRI of the brain at 6 months of age showed the prior findings along with globally decreased parenchymal volume. ABR performed at the same time showed moderate-severe sensorineural hearing loss (SNHL) bilaterally. Repeat echocardiogram at 6 months of age showed PFO, dilated coronary arteries, mild right atrial enlargement, muscular VSD, and mild concentric left ventricular hypertrophy with pulmonary hypertension and cardiomyopathy.

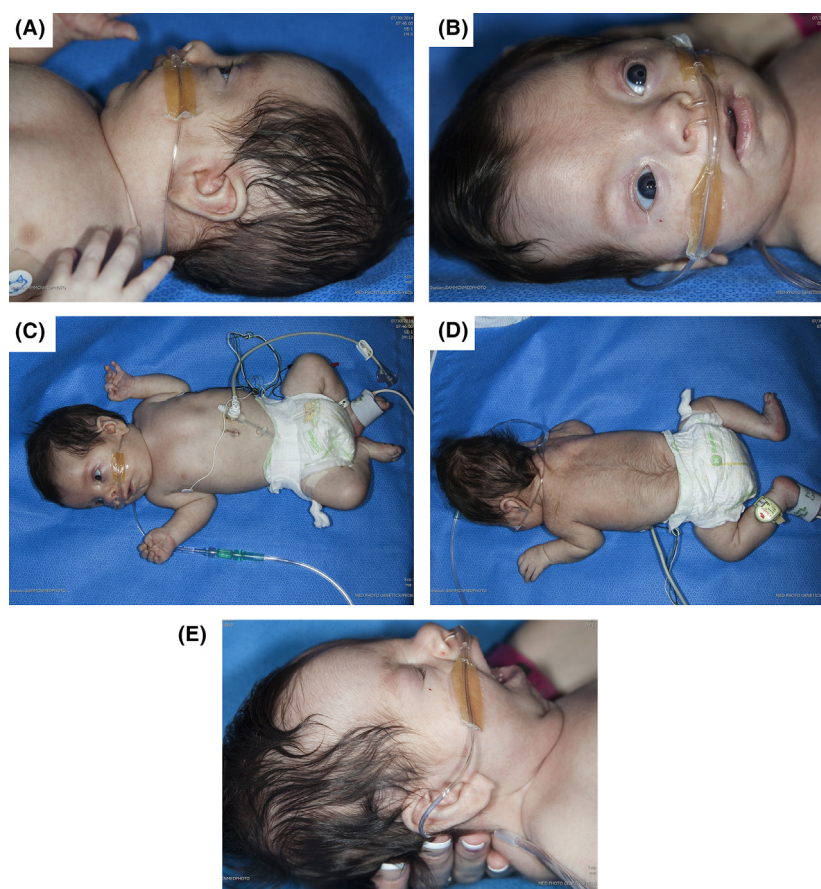


Figure 1. (A) Hypertrichosis. (B) Truncal hypotonia, widely spaced nipples. (C) Widened metopic suture, broad forehead, ocular hypertelorism, flat nasal bridge, bulbous nose, retrognathia, anteverted nares. (D) Micrognathia, short nose with anteverted nares. (E) Anteverted nares.

The patient is currently 14 months old and functioning developmentally at a 6–8 month level. He is babbling, waves goodbye, and is crawling. Most recent echocardiogram showed a muscular VSD that likely will not require any surgical intervention. ABR continued to show moderate hearing loss bilaterally requiring placement of hearing aids. MRI of the brain at 12 months did not show any changes from prior MRI at 6 months. He has had no seizure activity. He stills requires most feedings via a GJ tube.

Discussion

There exist within the literature limited reliable phenotypic comparisons between live-born mosaic trisomy 17 patients because many of the known cases with abnormal fetuses either terminated pregnancy early (i.e., [1, 4, 5, 8], offered limited medical description (Bullerdiek and Bartnitzke, 1982), or described potentially confounding clinical complications such as prematurity with sepsis and meningitis [6]. As of 2007, seven reported live-born cases

confirmed postnatally by fibroblast analysis demonstrated cerebellar hypoplasia (4/7), growth retardation (3/7), leg length/body asymmetry (3/7), and intellectual disability (5/7) [10]. Our patient exhibited many of the recurring medical and physical features already reported, along with notable additions (Table 1).

As above, our patient shared many features common to prior reported cases, further suggesting elements more common to the trisomy 17 mosaic phenotype, though many of these malformations are by no means specific to this diagnosis. In our case, of additional interest above supporting the thread of common features are those characteristics that have not yet been described in mosaic cases. Though this report cannot with certainty assess the likelihood of recurrence of these features, these descriptions contribute to the growing body of information for trisomy 17 mosaicism.

Our prognostic projections for trisomy 17 mosaicism and standing recommendations remain consistent with prior assertions. Diagnostic cordocentesis and lymphocyte analysis remain unlikely to yield valuable information that

Table 1. Feature in Mosaic Trisomy 17.

Symptoms and diagnoses	Physical features
Cystic hygroma*	Short stature*
IUGR*	Slow growth*
Single umbilical artery	Cryptorchidism*
SGA*	Progressive hypotonia*
Increased nuchal thickening	Microcephaly
Developmental delay*	Foot position abnormality*
Congenital tracheobronchomegaly*	Body asymmetry
Tracheobronchomalacia*	Large anterior fontanelle*
Chronic respiratory failure	Facial dysmorphism: facial
(tracheostomy dependence)*	asymmetry*, broad forehead*,
Gastrostomy tube dependence*	horizontal palpebral fissures*,
Dandy Walker variant*	ocular hypertelorism*,
Decreased parenchymal	short nose*, anteverted
brain volume*	nares*, abnormal ear lobes*,
Cerebellar and pontine	bulbous nose*,
hypoplasia*	micrognathia/retrognathia*
Moderate-severe SNHL	Wide spaced nipples*
Congenital heart disease:	Hypoplastic nails*
TOF, PFO*, VSD*,	
Dilated coronary arteries*,	Inguinal hernia*
concentric left ventricular	Nuchal redundancy*
hypertrophy*	
PPHN*	Postaxial polydactyly*
Cardiomyopathy*	Single palmar crease
Central hypothyroidism*	Hypertrichosis*
Hypoglycemia*	
Optic atrophy*	
Hydronephrosis*	
Adrenal insufficiency*	
Butterfly vertebrae*	
GERD*	
Intestinal malrotation	

*Features exhibited by our patient. Bold text indicates those features novel to our case and not previously reported [1, 3–9, 11].

would justify any additional costs associated with these interventions [8, 10]. The gold standard for postnatal diagnosis remains fibroblast analysis. This specimen karyotype proves to be a sensitive test with reassuring negative predictive value. However, the level of mosaicism does vary with tissue sample, and therefore does not correlate with prognosis [1, 10]. A normal ultrasound in the setting of a positive amniocentesis is a reassuring indicator, given that only one case has been reported with a normal ultrasound and trisomy 17 mosaicism at birth. Advanced ultrasound is therefore indicated, as this information serves most useful to stratify risk in patients [1, 12]. Prognosis is ultimately difficult to ascertain with such a small cohort, but interventions such as tracheostomy and gastrostomy tube placements may increase lifespan as seen with many other genetic conditions. The underlying maternal HELLP syndrome may have contributed to the

worsening respiratory distress and weight issues in the child but likely not to the dysmorphic features.

Acknowledgments

We thank the family and the patient for participation in this publication.

Disclosure

The authors have no conflict of interest to disclose, and there was no financial support. The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Air Force, Army, Department of Defense, nor the US Government. We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document and that each takes public responsibility for it.

References

- De Vries, F. A. T., L. C. P. Govaerts, J. Knijnenburg, M. F. C. M. Knapen, G. G. Oudesluijs, D. Lont, et al. 2013. Another rare prenatal case of post-zygotic mosaic trisomy 17. *Am. J. Med. Genet. A* 161A:1196–1199.
- Hassold, T. 1982. Mosaic trisomies in human spontaneous abortions. *Hum. Genet.* 61:31–35.
- Daber, R., K. A. Chapman, E. Ruchelli, S. Kasperski, S. Mulchandani, B. D. Thiel, et al. 2011. Mosaic trisomy 17: variable clinical and cytogenic presentation. *Am. J. Med. Genet. A* 155A:2489–2495.
- Genuardi, M., C. Tozzi, M. G. Pomponi, M. L. Stagni, M. Della Monica, G. Scaano, et al. 1999. Mosaic trisomy 17 in amniocytes: phenotypic outcome, tissue distribution, and uniparental disomy studies. *Eur. J. Hum. Genet.* 7:421–426.
- Lesca, G., D. Boggio, V. Bellec, J. P. Magaud, and M. Till. 1999. Trisomy 17 mosaicism in amniotic fluid cells not found at birth in blood but present in skin fibroblasts. *Prenat. Diagn.* 19:263–265.
- Shaffer, L. G., C. McCaskill, J. H. Hersch, F. Greenberg, and J. R. Lupski. 1996. A clinical and molecular study of mosaicism for trisomy 17. *Hum. Genet.* 97:69–72.
- Terhal, P., R. Sakkers, R. Hochstenbach, K. Madan, G. Rabelink, R. Sinke, et al. 2004. Cerebellar hypoplasia, sonular cataract, and peripheral neuropathy in trisomy 17 mosaicism. *Am. J. Med. Genet. A* 130:410–414.

8. Utermann, B., M. Riegel, D. Leistritz, T. Karall, J. Wisser, L. Meisner, et al. 2006. Pre- and postnatal findings in trisomy 17 mosaicism. *Am. J. Med. Genet. A* 140: 1628–1636.
9. Bullediek, J., and S. Bartnitzke. 1982. Hypotonic treatment in visual and automatic chromosome analysis. *Clin. Genet.* 22:150.
10. Collado, F. K., A. J. Fisher, and A. T. Bombard. 2003. Counseling patients with trisomy 17 mosaicism found at genetic amniocentesis. *Prenat. Diagn.* 23: 948–950.
11. Witters, I., M. Cannie, and J. P. Fryns. 2007. Prenatal diagnosis of trisomy 17 mosaicism. *Prenat. Diagn.* 27:677–678.
12. Hsu, L. Y., M. T. Yu, R. L. Neu, D. L. Van Dyke, P. A. Benn, C. L. Bradshaw, et al. 1997. Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20 and 21: karyotype/phenotype correlations. *Prenat. Diagn.* 17:201–242.